DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

JUL 14 2004

WARNING LETTER

Via Federal Express

Thomas L. Croley, M.D.
Central Florida Eye Institute
3133 SW 32nd Avenue
Ocala, Florida 34471

Dear Dr. Croley:

This Warning Letter informs you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. This Letter also discusses the March 23, 2004 written response from Ms. Diane M. Irwin, R.N., ASC Surgical Administrator, Central Florida Eye Institute, to the noted violations, and requests that you implement prompt corrective actions. Mr. Albertfiel A. Salvador and Ms. Brunilda Torres, investigators from FDA's Florida District Office (FLA-DO) and Ms. Contress Braxton, Consumer Safety Officer, of FDA's Center for Devices and Radiological Health (CDRH), conducted the inspection from March 8 through March 12, 2004. The purpose of the inspection was to determine whether your activities as a clinical investigator (CI) participating in the study entitled "[redacted]," sponsored by [redacted], complied with applicable FDA regulations. The [redacted] is a device as defined under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(h)].

The FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the Florida District Office revealed violations of Title 21, Code of Federal Regulations (21 CFR), Part 50 - Protection of Human Subjects and 21 CFR Part 812 - Investigational Device Exemptions. At the conclusion of the inspection, Ms. Torres presented a Form FDA 483 "Inspectional Observations" to you and [redacted] for review and discussed the listed deviations. The deviations noted on the Form FDA 483, our subsequent inspection report review, and Ms. Irwin's response to the Form FDA 483 items are discussed below:

Failure to obtain adequate informed consent (21 CFR Part 50 and 21 CFR 812.100).

Investigators are responsible for ensuring that informed consent (IC) is obtained in accordance with 21 CFR Part 50 and 21 CFR 812.100. Specifically, section 50.27(a) requires the informed consent to be signed and dated by the subject or the subject's legally authorized representative at the time of consent, and a copy be given to the person signing the form.

An example of your failure to comply with the IC requirements includes but is not limited to the following:

> A review of the records for all [redacted] study subjects revealed that the ICs were not dated by the subjects at the time of consent, nor were the subjects provided with a copy of the IC.
>
> [redacted] written response states that copies of the ICs were sent to all subjects involved in the study and verification of receipt of the ICs will be inserted in the patient's file as they become available. [redacted] also stated that the dates cannot be corrected due to it being after the fact; however, she states that "researchers" will correct this issue in future studies. Your correction appears to be acceptable.

Failure to conduct the study in accordance with the signed agreement, the investigational plan, and applicable FDA regulations (21 CFR 812.100, 21 CFR 812.110(b)).

You are required by FDA regulations to conduct your investigation in accordance with your signed agreement with the sponsor and the investigational plan, which includes the study protocol, as well as with FDA regulations. Our investigation revealed several deviations from the signed agreement and investigational plan, including but not limited to the following:

- The [redacted] protocol only allows for unilateral implants of the study [redacted] however, you implanted subject [redacted] with the study [redacted] in both eyes. Furthermore, a waiver from the sponsor was not obtained prior to the implantation of the second study [redacted] in that subject. According to the protocol, all implants must be performed with [redacted], must have the full knowledge and consent of a recognized IRB, and must conform with the sponsor's FDA-approved investigational plan.

  [redacted] written response states that the sponsor has been advised of the above situation. Please explain how you intend to prevent this from occurring in ongoing and future studies.

- The protocol required that fundus examinations be performed at both scheduled and unscheduled study visits; however, you failed to conduct the required fundus examinations for the following subjects: [redacted], and [redacted].

  [redacted] written response regarding the missing fundus exams states that all charts have been reviewed and corrected where possible, and copies have been made for the sponsor and IRB. Please explain how you intend to prevent this from occurring in ongoing and future studies.

- The protocol required that the adverse event report forms be completed and forwarded to the sponsor. You failed to complete and forward an adverse event form for a reportable adverse event experienced by subject [redacted], who was reported to have a clinical manifestation of macular edema in the operative eye at the [redacted] visit.

  [redacted] written response states that an adverse event form has been completed. However, it is not clear whether you have submitted the report to the sponsor, as required by the protocol. Please explain whether you have reported the adverse event to the sponsor, and how you intend to prevent this from occurring in ongoing and future studies.

Failure to report unanticipated adverse device effects (21 CFR 812.150).

You failed to report to the sponsor and IRB an unanticipated adverse device effect as required by 21 CFR 812.150(a)(1). As noted above, subject [redacted] was reported to have a clinical manifestation of macular edema in the operative eye.

We note that an adverse event form for this event has been completed. However, your response does not indicate whether the event was reported to the sponsor and IRB. Please clarify to whom you have reported this information.

Failure to maintain accurate, complete, and current records relating to your participation in the investigation (21 CFR 812.140(a)).

Pursuant to 21 CFR 812.140 (a), an investigator is required to maintain accurate, complete and current records relating to the investigator's participation in an investigation. Examples of your failure to adhere to this regulation include but are not limited to the following:

> A review of the subjects' records revealed that the case report forms (CRFs) did not contain information regarding complications and/or adverse effects experienced by subjects [redacted], [redacted], [redacted] and [redacted]. The sponsor instructed your site to document these events on the routine report forms. [redacted] written response regarding the CRFs states that all charts have been reviewed and corrected, and that copies have been made for the Sponsor and the IRB. Please explain how you intend to prevent this from occurring in ongoing and future studies.

Failure to prepare and submit complete, accurate, and timely reports to the sponsor, the monitor, and the reviewing IRB at regular intervals (21 CFR 812.150(a)(3)).

FDA regulations require an investigator to prepare and submit complete, accurate, and timely progress reports on the investigation to the sponsor, the monitor, and the IRB at regular intervals, but in no event less often than a year pursuant to (21 CFR 812.150(a)(3)). An example of your failure to comply with this provision includes but is not limited to the following:

> You failed to submit complete, accurate and timely progress reports to the Sponsor and the IRB on at least an annual basis. During the inspection, no annual progress report was observed on file nor had any reports been submitted for this study.
>
> [redacted] written response states that an annual progress report has been completed and submitted as of the date of her [redacted] response. Please explain how you intend to prevent this from occurring in ongoing and future studies.

The above-described deviations are not intended to be an all-inclusive list of deficiencies found in your clinical study. When conducting clinical investigations of products regulated by FDA, it is your responsibility to adhere to each requirement of the Act and applicable federal regulations.

Within fifteen (15) working days after receiving this letter, please provide written documentation of the additional, specific steps you have taken or will take to correct the violations and to prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 812.119.

Please send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2094 Gaither Road, Rockville, Maryland, 20850, Attention: Contress Braxton.

We are also sending a copy of this letter to FDA's Florida District Office, 555 Winderley Place, Maitland, Florida 32751, and request that you also send a copy of your response to that office. In addition, a copy of the progress report will be forwarded to Office of Device Evaluation (ODE). If you have any questions, please contact Ms. Braxton at (301) 594-4723, ext. 138 or by email at cmb@cdrh.fda.gov.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:
Purged Copies to:

IRB
Thomas L. Croley, M.D.
Chair, Institutional Review Board
Central Florida Eye Institute
3133 SW 32nd Avenue
Ocala, Florida 34474

Sponsor
[redacted]
President
[redacted]